Paper Alert

Chosen by Robert Liddington[1] and Christin Frederick[2]

A selection of interesting papers that were published in the month before our press date in major journals most likely to report significant results in structural biology.

Addresses: [1]Department of Biochemistry, University of Leicester, Leicester LE1 7RH, UK and [2]Laboratory of X-ray Crystallography, Dana-Farber Cancer Institute, 44 Binney Street, Boston, MA 02115, USA.

Structure 1996, Vol 4 No 10:1231–1233

☐ Structure of the FGF receptor tyrosine kinase domain reveals a novel autoinhibitory mechanism. Moosa Mohammadi, Joseph Schlessinger and Steven R Hubbard (1996). *Cell* 86, 577–587.

Growth factors play important roles in the control of cell growth, differentiation, metabolism, and oncogenesis. Their diverse biological effects are mediated by a large family of cell surface receptors with intrinsic protein tyrosine kinase (PTK) activity. The crystal structure of the tyrosine kinase domain of fibroblast growth factor receptor 1 (FGFR1K) is determined in its unliganded form to 2.0 Å resolution and in complex with an ATP analog to 2.3 Å resolution. Several features distinguish the structure of FGFR1K from that of the tyrosine kinase domain of the insulin receptor. Residues in the activation loop of FGFR1K appear to interfere with substrate peptide binding but not with ATP binding, revealing a second and perhaps more general autoinhibitory mechanism for receptor tyrosine kinases.

23 August 1996, *Cell*

☐ Crystal structure of L-2-haloacid dehalogenase from ***Pseudomonas*** sp.YL. Tamao Hisano, Yasuo Hata, Tomomi Fujii, Ji-Quan Liu, Tatsuo Kurihara, Nobuyoshi Esaki and Kenji Soda (1996). *J. Biol. Chem.* 271, 20322–20330.

L-2-haloacid dehalogenase catalyzes the hydrolytic dehalogenation of L-2-haloalkanoic acids to yield the corresponding D-2-hydroxyalkanoic acids. The crystal structure of the homodimeric enzyme from *Pseudomonas* sp. YL has been determined at 2.5 Å resolution. The subunit consists of two structurally distinct domains: the core domain has an α/β structure formed by a six-stranded parallel β sheet flanked by five α helices and the subdomain inserted into the core domain has a four helix bundle structure. There is an active site cavity between the domains. Although the enzyme is an α/β-type hydrolase, it does not belong to the α/β hydrolase fold family, since the topology and location of the nucleophile are different.

23 August 1996, *The Journal of Biological Chemistry*

☐ A fast flexible docking method using an incremental construction algorithm. Matthias Rarey, Bernd Kramer, Thomas Lengauer and Gerhard Klebe (1996). *J. Mol. Biol.* 261, 470–489.

The authors present an automatic method for docking ligands into protein-binding sites. It combines an appropriate model of the physicochemical properties of the docked molecules with efficient methods for sampling the conformational space of the ligand. If the ligand is flexible, it can adopt a large variety of different conformations. Results are presented on 19 complexes of which the binding geometry has been crystallographically determined. All considered ligands are docked in three minutes at most on a current workstation. The experimentally observed binding mode of the ligand is reproduced with 0.5 to 1.2 Å rms deviation. It is almost always found among the highest-ranking conformations computed.

23 August 1996, *Journal of Molecular Biology*

☐ How proteins recognize the TATA box. Zong Sean Juo, Thang Kien Chiu, Paul M Leiberman, Igor Baikalov, Arnold J Berk and Richard E Dickerson (1996). *J. Mol. Biol.* 261, 239–254.

The crystal structure of a complex of human TATA-binding protein with TATA-sequence DNA has been solved, complementing earlier TBP–DNA analyses from *Saccharomyces cerevisiae* and *Arabidopsis thaliana*. Special insight into TATA-box specificity is provided by considering the TBP–DNA complex not as a protein molecule with bound DNA but as a DNA duplex with a particularly large minor groove ligand. This point of view provides explanations for biochemical observations regarding the various sequence requirements for the interaction.

16 August 1996, *Journal of Molecular Biology*

☐ A structure-based catalytic mechanism for the xanthine oxidase family of molybdenum enzymes. Robert Huber, Peter Hof, Rui O Duarte, Jose JG Moura, Isabel Moura, Ming-Yih Liu, Jean LeGall, Russ Hille, Margarida Archer and Maria J Romão (1996). *Proc. Natl. Acad. Sci. USA* 93, 8846–8851.

Molybdenum-containing hydroxylases catalyze the incorporation of oxygen derived from water into substrates in a manner whereby reducing equivalents are generated rather than consumed. The crystal structure of a xanthine oxidase-related molybdenum-iron protein, aldehyde oxidoreductase, from the sulfate-reducing anaerobic Gram-negative bacterium *Desulfovibrio gigas* (Mop), was analyzed in its desulfo-, sulfo-, oxidized, reduced, and alcohol-bound forms at 1.8 Å resolution. This series of structures allows the authors to propose a complete reaction pathway for enzymes of this type.

20 August 1996, *Proceedings of the National Academy of Sciences of the USA*

□ The solution structure of the Raf-1 cysteine-rich domain: a novel Ras and phospholipid binding site. Helen R Mott, John W Carpenter, Sheng Zhong, Sujoy Ghosh, Robert M Bell and Sharon L Campbell (1996). *Proc. Natl. Acad. Sci. USA*. 93, 8312–8317.

The Raf-1 protein kinase is the best-characterized downstream effector of activated Ras. Interaction with Ras leads to Raf-1 activation and results in transduction of cell growth and differentiation signals. The authors have determined the solution structure of the cysteine-rich domain (CRD) of Raf-1. There are differences between the structure of Raf-1CRD and the structures of two related domains from protein kinase C (PKC). These differences are confined to regions of the CRDs involved in binding phorbol ester in the PKC domains.
6 August 1996, *Proceedings of the National Academy of Sciences of the USA*

□ Crystal structure of Δ^9 stearoyl-acyl carrier protein desaturase from castor seed and its relationship to other di-iron proteins. Ylva Lindqvist, Weijun Huang, Gunter Schneider and John Shanklin (1996). *EMBO J.* 15, 4081–4092.

The crystal structure of homodimeric Δ^9 stearoly-acyl carrier protein desaturase, the archetype of the soluble plant fatty acid desaturases that convert saturated to unsaturated fatty acids, has been determined at 2.4 Å. The 363 amino acid monomer consists of a single domain of 11 α helices. Nine of these form an antiparallel helix bundle. The enzyme subunit contains a di-iron centre with ligands from four of the α helices in the helix bundle. A deep channel which probably binds the fatty acid extends from the surface into the interior of the enzyme. Modelling of the substrate, stearic acid, into this channel places the Δ^9 carbon atom in the vicinity of one of the iron ions.
15 August 1996, *The EMBO Journal*

■ Crystal structure of a PDZ domain. João H Morais Cabral, Carlo Petosa, Michael J Sutcliffe, Sami Raza, Olwyn Byron, Florence Poy, Shirin M Marfatia, Athar H Chishti and Robert C Liddington (1996). *Nature* 382, 649–652.

PDZ domains (also known as DHR domains or GLGF repeats) are ~90-residue repeats found in a number of proteins implicated in ion-channel and receptor clustering, and the linking of receptors to effector enzymes. PDZ domains are protein-recognition modules which recognize either the consensus C-terminal tripeptide motif S/TXV or other PDZ domains. The crystal structure of the third PDZ domain of the human homologue of the *Drosophila discs-large* tumour-suppressor gene product, DlgA, consists of a five-stranded antiparallel β barrel flanked by three α helices. A groove runs over the surface of the domain, ending in a conserved hydrophobic pocket and a buried arginine. The authors suggest that this is the binding site for the C-terminal peptide, and this was confirmed by the structure of the related domain from PSD-95 (Doyle *et al*. *Cell* 85, 1067–1076 [1996]).
15 August 1996, *Nature*

□ Structure of the WW domain of a kinase-associated protein complexed with a proline-rich peptide. Maria J Macias, Marko Hyvönen, Elena Baraldi, Johan Schultz, Marius Sudol, Matti Saraste and Hartmut Oschkinat (1996). *Nature* 382, 646–649.

The WW domain is a new protein module with two highly conserved tryptophans that binds proline-rich peptide motifs *in vitro*. It is present in a number of signalling and regulatory proteins, often in several copies. This paper describes the solution structure of the WW domain of human YAP65 in complex with proline-rich peptides containing the core motif PPxY. The structure of the domain is a slightly curved, three-stranded, antiparallel β sheet. The structure of the WW domain differs from that of the SH3 domain and reveals a new design for a protein module that uses stacked aromatic surface residues to arrange a binding site for proline-rich peptides.
15 August 1996, *Nature*

□ The role of the divalent cation in the structure of the I domain from the CD11a/CD18 integrin. Aidong Qu and Daniel J Leahy (1996). *Structure* 4, 931–942.

The integrin family of cell-surface receptors mediates a wide variety of cell–cell and cell–extracellular matrix interactions. A subset of integrins contain an ~200 amino acid inserted (I) domain that is important for ligand-binding activity and contains a single divalent cation binding site. Many integrins are believed to respond to stimuli by undergoing a conformational change that increases their affinity for ligand. This paper reports the crystal structures of the CD11a I domain determined in the absence of bound metal ion and with bound magnesium ion. The structures of the CD11a I domain with magnesium or manganese bound are extremely similar and no major rearrangements occur in the absence of bound metal. These results are compared with results on the CD11b domain, in which large conformational changes were observed in the presence of different metals; however, they do not directly address the issue of activation.
15 August 1996, *Structure*

□ Synchrotron X-ray studies suggest that the core of the transthyretin amyloid fibril is a continuous β-sheet helix. Colin Blake and Louise Serpell (1996). *Structure* 4, 989–998.

Amyloid diseases, which include Alzheimer's disease and the transmissible spongiform encephalopathies, are characterized by the extracellular deposition of abnormal protein fibrils derived from soluble precursor proteins. The structure at 2.0 Å resolution of amyloid fibrils from patients with familial amyloidotic polyneuropathy (FAP), which are derived from transthyretin (TTR) variants, was investigated by fibre diffraction methods

■ See the Minireview article by David Cowburn in the 15 September issue of *Structure* (volume 4:1005–1008).

using synchrotron radiation. This work suggests that amyloid fibrils have a novel molecular structure consisting of β sheets extended in regular helical twists along the length of the fibre. This implies that the polypeptide chains in the fibres are hydrogen bonded together along the entire length of the fibres, thereby accounting for their great stability. The proposed structure of the FAP fibril suggests that amyloid formation may require significant structural change in precursor proteins.
15 August 1996, *Structure*

☐ The structure of aquareovirus shows how the different geometries of the two layers of the capsid are reconciled to provide symmetrical interactions and stabilization. Andrea L Shaw, Siba K Samal, K Subramanian and BV Venkataram Prasad (1996). *Structure* 4, 957–967.

Aquareoviruses are pathogens of aquatic animals and belong to the family Reoviridae. A structural feature common to members of the Reoviridae is a multilayered capsid, formed by several concentric icosahedral shells with different protein compositions. The three-dimensional structure of aquareovirus to 23 Å resolution was determined using electron cryomicroscopy. The structure displays marked similarity to the mammalian reovirus intermediate subviral particles, suggesting a close evolutionary relationship. However, a noticeable distinction is that aquareovirus lacks the hemagglutinin spike observed in reovirus.
15 August 1996, *Structure*

☐ The structure of an RNA dodecamer shows how tandem U–U base pairs increase the range of stable RNA structures and the diversity of recognition sites. Susan E Lietzke, Cindy L Barnes, J Andrew Berglund and Craig E Kundrot (1996). *Structure* 4, 917–930.

Non-canonical base pairs are fundamental building blocks of RNA structures. They can adopt geometries quite different from those of canonical base pairs and are common in RNA molecules that do not transfer sequence information. Tandem U–U base pairs occur frequently, and can stabilize duplex formation despite the fact that a single U–U base pair is destabilizing. The authors determined the crystal structure of the RNA dodecamer GGCGCUUGCGUC at 2.4 Å resolution. The molecule forms a duplex containing tandem U–U base pairs, which introduce an overall bend of 11–12° in the duplex resulting from conformational changes at each interface between the tandem U–U base pairs and a flanking duplex sequence.
15 August 1996, *Structure*

☐ The CD4 determinant for downregulation by HIV-1 Nef directly binds to Nef. Mapping of the Nef binding surface by NMR. Stephan Grzesiek, Stephen J Stahl, Paul T Wingfield and Ad Bax (1996). *Biochemistry* 35, 10256–10261.

HIV-1 Nef is a 206-residue, N-terminal myristylated and membrane-associated protein that is expressed at high levels in the early stages of HIV infection. Using heteronuclear NMR spectroscopy, the authors demonstrated that a 13-residue peptide (MSQIKRLLSEKKT) from the cytoplasmic tail of CD4 binds to Nef protein. The peptide-binding site has been mapped onto the previously determined solution structure of HIV-1 Nef on the basis of peptide induced chemical shift changes.
13 August 1996, *Biochemistry*

☐ The 2.8 Å structure of a *T*=4 animal virus and its implication for membrane translocation of RNA. Sanjeev Munshi, Lars Liljas, Jean Cavarelli, Wu Bomu, Bonnie McKinney, Vijay Reddy and John E Johnson (1996). *J. Mol. Biol.* 261, 1–10.

The paper describes the first atomic resolution structure of a *T*=4 RNA virus. The structure reveals prefabricated helical bundles on the fivefold axes nearly identical to those observed in the *T*=3 nodaviruses. These bundles may serve as conduits for RNA membrane translocation. The helices are of sufficient length to span a membrane bilayer and the internal diameter of the coiled bundle could accommodate ssRNA.
9 August 1996, *Journal of Molecular Biology*

☐ Structural basis for inhibition of receptor protein-tyrosine phosphatase-α by dimerization. Alexandrine M Bilwes, Jeroen den Hertog, Tony Hunter & Joseph P Noel (1996). *Nature* 382, 555–559.

Receptor-like protein-tyrosine phosphatases (RPTPs) regulate the level of phosphotyrosine-containing proteins derived from the action of protein-tyrosine kinases. RPTPs are type-I internal membrane proteins that contain one or two catalytic domains in their cytoplasmic region. This paper describes the crystal structure of the membrane-proximal catalytic domain (D1) of a typical RPTP, murine RPTPα. Significant structural deviations from the PTP1B fold occur in the N-terminal part of the domain. An N-terminal segment inserts into the active site of a dyad-related D1 monomer. The authors propose that dimerization and active-site blockage is a mechanism for downregulating the catalytic activity of RPTPα and other RPTPs.
8 August 1996, *Nature*

☐ Structural basis of cyclin-dependent kinase activation by phosphorylation. Alicia A Russo, Philip D Jeffrey and Nikola P Pavletich (1996). *Nat. Struct. Biol.* 3, 696–700.

Cyclin-dependent kinase (CDK)-cyclin complexes require phosphorylation on the CDK subunit for full activation of their Ser/Thr protein kinase activity. The crystal structure of the phosphorylated CDK2–CyclinA–ATPγS complex has been determined at 2.6 Å resolution. The phosphate group, which is on the regulatory T-loop of CDK2, is mostly buried, its charge being neutralized by three arginine side chains. The arginines help extend the influence of the phosphate group through a network of hydrogen bonds to both CDK2 and cyclinA. Comparison with the unphosphorylated CDK2–CyclinA complex shows that the T-loop moves by as much as 7 Å, and this affects the putative substrate-binding site as well as resulting in additional CDK2–CyclinA contacts. The phosphate group thus acts a a major organizing centre in the CDK2–CyclinA complex.
August 1996, *Nature Structural Biology*